## REMARKS

Claims 29-34 are currently pending in the application. In order to advance prosecution, Applicants have amended claim 29 to more particularly point out and distinctly and clearly claim their invention. A complete listing of all the claims, in compliance with the revised amendment format, is shown above. The amendments to the pending claims are made in order to expedite the issuance of the claims. The amendments are made without prejudice, do not constitute amendments to overcome any prior art rejection, and do not present any new matter.

### Discussion of Claim Objections

Claim 29 is objected to for using the abbreviation "OD" without first spelling the term in its entirety. Applicants have amended claim 29, and thereby respectfully request withdrawal of these objections.

### Discussion of the 35 U.S.C. § 112, paragraph 2 Rejection

Claims 30, 32, and 34 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite because it is not clear if ABX-0303 refers to a single antibody species or to a genus of antibodies. The Office Action acknowledges that the specification refers to U.S. Patent 6,235,883 ("the '883 patent") for teaching the ABX-0303 antibody, and that the '883 patent provides the methods for making antibodies and for providing the structures of antibodies, such as the antibody that corresponds to ABX-0303. However, the Office Action alleges that the '883 patent describes 8 different antibodies, and that it is therefore unclear what the scope of the claims is. Applicants respectfully traverse the rejection. Applicants agree that the '883 patent



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teaches multiple hybridoma cell lines that produce antibodies. However, Applicants respectfully point out that the present specification does explain that "ABX-0303 is described in detail in U.S. Patent No. 6,235,883 (the disclosure of which is hereby incorporated by reference) and referred to therein in connection with the discussions related to *hybridoma E7.6.3*." *See* Application at 16, lines 24-26 (emphasis added). As such, the specification does make clear the scope of the claims, as ABX-0303 refers to the antibodies referred to in the '883 patent in connection with the discussions related to hybridoma E7.6.3. As such, Applicants respectfully contend that this asserted ground for rejection has been overcome, and therefore requests reconsideration and withdrawal of the rejection.

**Discussion of the 35 U.S.C. § 112, paragraph 1 Rejection**

Claims 29-34 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which is not set forth in such a way as to enable one skilled in the art to make and/or use the invention. The Office Action alleges that the specification does not reasonably provide enablement for treating a subject with any type of cancer comprising first selecting a patient population using the method recited in the claims and the cut-off for selection recited in the claims. The Office Action further alleges that the limited disclosure of the specification and the use of the specific optical density cut-off assessing responsiveness to an anti-EGFR antibody do not appear to enable the broad scope of the claims. This rejection is respectfully traversed.

Under 35 U.S.C. § 112, all that is required is that the specification describe the invention in such terms as to enable a person skilled in the art to make and use the invention. Thus, to enable claims 29-34, the specification must teach one skilled in the art how to make and use a



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method of treating a subject with cancer comprising cells that express EGFR, in part, by treating the subject with an anti-EGFR antibody if HER3 expression levels are detected having an optical density less than 9 when determined by quantitative immunohistochemistry. The test of enablement is whether one reasonably skilled in the art (1) could make and use the invention (2) from the disclosures in the application coupled with information known in the art (3) without undue experimentation. M.P.E.P. § 2164.01; *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988); *United States v. Telectronics*, Inc., 857 F.2d 778 (Fed. Cir. 1988).

Contrary to the Office Action's allegation, the specification provides considerable guidance to enable a skilled artisan to make and use methods that utilize, in part, HER3 expression levels that are detected having an optical density less than 9 when determined by quantitative immunohistochemistry. The Office Action's allegations hinge on the cited Esteva article, which according to the Office, uses "much lower cut-offs for determining high versus low levels of tumor markers than what is recited in the specification." Even while acknowledging that optical density measurements are arbitrary units, the Office summarily concludes that "Esteva appears to use a method similar to that described in the instant specification." Therefore, according to the Office, "[t]here is no indication in the specification nor in the prior art that the results using a cut-off of optical density of less than 9 would be appropriate for cancers other than renal cancer as exemplified in the specification."

Applicants first respectfully point out that the quantitative immunohistochemistry described in Esteva was not concerned with determining whether a subject with cancer comprising cells that express EGFR should be treated with an anti-EGFR antibody. Instead, Esteva was concerned with determining the *frequency of expression* of the various biomarkers,



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including HER3, and *identifying associations of coexpression* between these proteins. As such, the desired results between the methods described in the present specification and that of Esteva are completely different. Thus, not only is the cut-off used by Esteva not relevant to the present case, it is entirely inappropriate to import Esteva's cut-off standards.

Nevertheless, Applicants respectfully point out that the present specification contains methods for quantitative immunohistochemistry that would enable a person skilled in the art to make and use the present invention. The Office Action has not adequately demonstrated why an optical density less than 9 is an inappropriate cut-off for identifying subjects that should be treated with an anti-EGFR antibody when the methods as described in the specification are used. Instead, the Office Action compares those methods to a method described in a completely unrelated reference. The Office Action is correct in stating that the method described in Esteva is "similar" to the methods described in the present specification – in that they both use monoclonal antibodies (although Esteva describes using antibodies purchased from Santa Cruz Biotechnology, while the specification teaches HER3 antibodies such as SGP1); they both stained and counterstained the paraffin-imbedded tumor sample; and they both used image analysis to quantify the results. However, the similarities do not extend much beyond these basics shared by all quantitative immunohistochemical methods. As an example, in Esteva, HER3 is stained with alkaline phosphatase, and counterstained with CAS Dna (QDL) stain. *See Esteva*, pg. 173, col. 1. On the other hand, one of the examples in the present specification discusses counterstaining HER3 with 4% ethyl green (Sigma). *See Application* at 12, lines 16-18. The Office Action has not attempted to explain how this difference would affect the observed OD, or provide any documentary support that the different staining procedures would



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yield corresponding OD values, much less explain why any of the other differences between Esteva and the specification would not result in differences to the OD values. The Office Action has basically ignored all of the specifics of the various methods taught not only in the examples, but in the specification as a whole. Moreover, the Office Action has not explained, nor provided any support, why, based on the methods found in the specification, an optical density less than 9 would be in inappropriate cut-off.

Applicants respectfully request reconsideration and withdrawal of the rejection.

**Discussion of the 35 U.S.C. § 103 Rejections**

Claims 29, 31 and 33 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,770,195 ("Hudziak") in view of Esteva, F.J. *et al.*, Pathology Oncology Research, 7(3): 171-177, 2001 ("Esteva"). The Applicants respectfully traverse the rejection.

An analysis for obviousness requires a determination of the scope and content of the prior art, the differences between the prior art and the claims at issue must be ascertained, and the level of ordinary skill in the pertinent art must be resolved. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). The Supreme Court again recently reaffirmed the primacy of the *Graham* approach for analyzing obviousness in *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007). In particular, the *KSR* case reaffirmed the requirement that the analysis must be made explicit when articulating an obviousness rejection based on a combination of the prior art. *See KSR v. Teleflex*, 127 S. Ct. 1727, 1740 (2007), citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness."). The Patent Office's Guidelines following *KSR*



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confirm that to establish obviousness the Office must identify *a reason* why one of ordinary skill in the art would make the claimed invention and there must be *predictability* in the result. M.P.E.P. § 2131(I)-(III)

The instantly claimed invention is directed in part to methods for treating a subject with cancer comprising cells that express EGFR. These methods include, in part, the step of assaying a cell or tissue sample from the subject to detect an expression level for HER3 in cells from the cancer. Moreover, these methods, in part, require treating the subject with an anti-EGFR antibody if HER3 expression levels are detected having an optical density less than 9 when determined by quantitative immunohistochemistry. It is important to note that EGFR is otherwise known as HER1, and is a different and distinct protein from HER3.

None of the cited references, either alone or in combination, teach or suggest the instantly claimed methods. The Office Action only cites to Hudziak as disclosing a method of treating cancer that express EGFR with an anti-EGFR antibody. Hudziak also discloses methods of treating tumor cells with antibodies that inhibit growth factor receptor function. *Hudziak* at Abstract. However, even the Office Action concedes that Hudziak does not teach treating a subject with an anti-EGFR antibody if HER3 expression levels are detected having an optical density less than 9 when determined by quantitative immunohistochemistry. In fact, Hudziak does not even disclose the existence of HER3, much less its use as a biomarker. As such, Hudziak certainly does not disclose the use of HER3 as a biomarker for the use of an anti-EGFR antibody. Therefore, Hudziak does not teach or even suggest the presently claimed invention.

The deficiencies of Hudziak are not overcome by the combination with Esteva. Esteva is cited as disclosing measurement of the levels of EGFR, HER2, HER3, HER4, hergulin, p38, and



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pHER2. Esteva does, in fact, disclose measurement of the levels of protein markers from 35 evaluable cancer patients. *See Esteva*, at 173, col. 2. In addition, Esteva identified correlations between the various protein markers. *See id.* at 173, col. 2-174, col. 1. Moreover, Esteva identified additional correlations to some of the protein markers, including correlations with age and tumor size. *See id.*, at 173, col. 2. However, Esteva does not teach or suggest that any of these patterns of expression and/or activation can be used to select a subject with cancer for treatment with a molecule targeting EGFR (indeed, this correlation is not provided even for tumors expressing EGFR itself). Esteva certainly does not teach or suggest treating a subject with an anti-EGFR antibody if HER3 expression levels are detected having an optical density less than 9 when determined by quantitative immunohistochemistry. In fact, the Office Action does not even allege that Esteva contains such a disclosure. Therefore, Esteva certainly does not teach the presently claimed invention.

The Office Action argues that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the methods of Esteva to measure levels of HER3 prior to treating a patient with an anti-EGFR antibody because Esteva teaches that HER3 is known to be associated with insensitivity to chemotherapeutic agents. However, it does not follow that just because expression of HER3 might correlate with an *insensitivity* to chemotherapeutic agents in general, that low expression of HER3 would necessarily result in *sensitivity* to non-specific chemotherapeutic agents, much less sensitivity to a specific anti-EGFR antibody. The Office Action continued by alleging that this insensitivity to chemotherapeutic agents provides the motivation to combine these two teaching, apparently because anti-EGFR antibodies are often used together with chemotherapeutic agents in the treatment of cancer.



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However, it cannot be ignored that the claims do not require the use of multiple chemotherapeutic agents, but instead require that HER3 expression levels be used to identify subjects to treat with anti-EGFR antibodies.

Moreover, the Office Action alleges that one of skill in the art would have been motivated to make and use the present invention in view of the fact that Esteva teaches that "HER-3 is known to be activated by ligands for other HER receptors, such as EGF and betacellulin." However, even if this assumption regarding the teaching of Esteva is true, a point which is not conceded, Esteva would teach away from the claimed invention. If, in fact, Esteva teaches that HER3 is activated by ligands that are specific for the HER receptor, than one of skill in the art would have concluded that *high levels* of HER3 expression would have identified subjects to treat with anti-EGFR antibodies. This is because a skilled artisan would have understood that if HER3 is know be activated by ligands for EGFR, then HER-3 likely or possibly also reacts with anti-EGFR antibodies. However, the present application was the first to teach that it was actually lower levels of expression of HER3 that can be used to identify these subjects. Therefore, if Esteva does, in fact, teach that HER3 is activated by ligands for other HER receptors, as alleged by the Office Action, than it necessarily teaches away from the claimed invention.

Applicants respectfully submit that the Office Action has not provided any legitimate *reason* why the references would have rendered the instantly-claimed invention predictable to one skilled in the art, or specifically why it would have been *predictable* to the skilled artisan that HER3 would be a negative predictor of a response to an anti-EGFR antibody even if these two references were combined. As such, Applicants respectfully contend that the Office Action



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has failed to establish a *prima facie* case of obviousness because first, a skilled artisan would not have been motivated to combine these two references, and second, even if the references were improperly combined, all of claim limitations are not even taught or suggested by the combination of Hudziak and Esteva.

Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

Claims 29-34 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hudziak in view of Esteva and further in view of Yang, W.-D *et al.*, Critical Reviews on Oncology/Hematology, 38: 17-23 (2001) ("Yang"). The Applicants traverse the rejection.

As explained above, the combination of references cited by the Patent Office does not teach, suggest, or make obvious all of the claims limitations of claim 29. The combination of references does not teach, disclose or make obvious at least the following limitation of claim 29: "treating the subject with an anti-EGFR antibody if HER3 expression levels are detected having an optical density less than 9 when determined by quantitative immunohistochemistry."

The additionally cited reference, taken alone or in any combination with the earlier-discussed references, do not teach or suggest the instantly claimed method. The teachings and deficiencies, as related to the present invention, of Hudziak and Esteva are thoroughly discussed above. The deficiencies of Hudziak and Esteva are not overcome by the combination with Yang. In this ground of rejection, Yang is cited additionally as teaching the ABX-0303 antibody. However, Yang does not teach or suggest that HER3 can be used as a biomarker for the use of the ABX-0303, much less treating a subject with ABX-0303 if HER3 expression levels are



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detected having an optical density less than 9 when determined by quantitative immunohistochemistry.

As a result, Yang's combination with Hudziak and Esteva can not teach or suggest all of the claim limitations. Thus, the Patent Office has not established a *prima facie* case of obviousness of claim 29 based on the cited references. As rejected claims 30-34 depend from claim 29, thereby sharing the above limitations, the cited references also cannot render these claims obvious. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

## CONCLUSION

Based on all of the above, the Applicants believe the claims are now allowable. If there are any questions or comments regarding this response, the Patent office is encouraged to contact the undersigned agent as indicated below.

Respectfully submitted,

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